

the invention. Specifically, the Examiner says that the metes and bounds of this claim is not defined as it recites an open-ended Markush group.

Applicants have amended claim 53 to recite a closed Markush group to overcome this rejection and thus, respectfully request the withdrawal of this rejection to claim 53.

Rejections Under 35 U.S.C. §103(a)

Claims 36-55 are rejected under 35 U.S.C. §103(a) as being unpatentable over Heller et al. (Heller), in view of Guttman et al. (Guttman). Specifically, the Office action alleges that it would be *prima facie* obvious to one of skill in the art to modify the device of Heller to use Guttman's lithium acetate buffer, resulting in the current invention. The Examiner alleges that Guttman provides the motivation to combine by teaching the importance of the lithium buffer's pH for molecular sieving and for improvement of quantitative data. The Examiner also further alleges that, regarding current claim 42 which defines the concentration of lithium at "about 0.1M", the selection of one lithium concentration over another is routine optimization. Applicants respectfully disagree with these allegations and provide their reasons below.

Heller discloses a microelectronic device that detects molecular interactions between oligonucleotide probes and target nucleic acids using fluorescence and optical detection. That is, Heller uses the electrodes to do electrophoresis to bring down the target nucleic acid to bind to the probes on the surface. However, detection of hybridization is based on fluorescence, not electronics. Thus, Heller does not have an electrical detector connected to the microelectrodes.

Heller does not teach or suggest the use of lithium in the device nor does it disclose electrical detection.

Guttman teaches electrophoretic separation (molecular sieving) for profiling oligosaccharides released from glycoproteins in a medium that includes lithium acetate. Guttman teaches fluorescence detection, not electrical detection, and does not teach or disclose the use of lithium for electrical detection.

The current invention measures molecular interactions between an immobilized probe (nucleic acid or peptide) and a target nucleic acid without reporters and measures such interaction electrically. Detection is done using lithium ions from the electrolyte buffer to provide a change in the electrical signal, for example, a change in AC impedance (see specification, page 4, lines 14-17).

As the Examiner is aware, the test for obviousness is whether the claimed invention as a whole would have been obvious at the time it was made to a person of ordinary skill in the art. A *prima facie* case of obviousness requires that (1) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (2) there should be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations. See M.P.E.P. § 2142.

Applicants submit that neither Heller nor Guttman, taken alone or in combination, provide the motivation to combine. In particular, Guttman's teaching regarding the use of a lithium acetate buffer for electrophoresis of oligosaccharides would not motivate one of skill in

the art to combine it with Heller's device which uses nucleic acids since neither reference suggests the use of lithium buffer for electrophoresis of nucleic acids. That is, since oligosaccharides and nucleic acids are chemically distinct species, use of lithium buffer with nucleic acids, even for electrophoresis, is not obvious to a person of skill in the art unless explicitly mentioned in either reference. Applicants respectfully remind the Examiner that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); M.P.E.P. § 2143.01. Absent evidence of explicit motivation to combine the references, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Applicants also submit that, even if improperly combined, Heller's apparatus with the lithium buffer would not be functional in the manner in which the Examiner suggests. Neither Heller nor Guttman disclose or suggest electrical detection and teach fluorescence detection instead. The suggested combination would at the most result in the use of Guttman's lithium buffer in Heller's device for measuring fluorescence. Applicants submit that the Examiner is using hindsight reconstruction from the Applicants' disclosure to piece together teachings from the prior art to result in the claimed invention. Applicants respectfully remind the Examiner that "[I]t is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious", *In re Fritch*, 23 USPQ2d 1780, 1784 (CAFC 1992). Thus, the suggested combination, besides being improper, does not provide a reasonable expectation of success.

Applicants also submit that all the claim limitations are not taught. As submitted by the Examiner and as discussed above, neither Guttman nor Heller teach electrical detection or the importance of lithium for reporterless electrical detection. Hence, the combination does not teach all the claim limitations.

Regarding claim 42, Applicants note that Guttman optimizes the buffer's pH using lithium for optimal molecular sieving. Also, Guttman's emphasis on lithium's pH in molecular sieving does not teach one of skill in the art to routinely experiment with lithium's concentration for optimal reporterless electrical detection. Thus, the selection of one lithium concentration over another for optimal signal amplification would not be considered routine in this case. Thus, Applicants submit that the combination of Heller and Guttman does not anticipate claim 42.

In view of the above remarks, Applicants submit that a *prima facie* case of obviousness has not been established. Thus, Applicants respectfully request withdrawal of the rejection of claims 36-55 under 35 U.S.C 103(a).

CONCLUSION

Applicants respectfully submit that claims 36-55 are now in condition for allowance and an early notification of such is requested.

Serial No. 09/458,533
Filed December 9, 1999

The Examiner is invited to call the undersigned attorneys for discussion of any outstanding issues.

Respectfully submitted,

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Dated: 10/1/02

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